

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE  
in its capacity as elected Office

Date of mailing (day/month/year) 22 February 2001 (22.02.01)	
International application No. PCT/US00/14743	Applicant's or agent's file reference 205271
International filing date (day/month/year) 26 May 2000 (26.05.00)	Priority date (day/month/year) 28 May 1999 (28.05.99)
Applicant KELLER, Gregory, S. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
21 December 2000 (21.12.00)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

AXFORD, Laurie, A.  
Morrison & Foerster LLP  
Suite 500  
3811 Valley Centre Drive  
San Diego, CA 92130-2332  
ETATS-UNIS D'AMERIQUEDate of mailing (day/month/year)  
23 October 2001 (23.10.01)Applicant's or agent's file reference  
514072000140

## IMPORTANT NOTIFICATION

International application No.  
PCT/US00/14743International filing date (day/month/year)  
26 May 2000 (26.05.00)

## 1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

## Name and Address

LARCHER, Carol  
Leydig, Voit & Mayer, Ltd.  
Suite 4900  
Two Prudential Plaza  
180 North Stetson  
Chicago, IL 60601-6780  
United States of America

## State of Nationality

## State of Residence

## Telephone No.

312 616 5600

## Facsimile No.

312 616 5700

## Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

## Name and Address

AXFORD, Laurie, A.  
Morrison & Foerster LLP  
Suite 500  
3811 Valley Centre Drive  
San Diego, CA 92130-2332  
United States of America

## State of Nationality

## State of Residence

## Telephone No.

858 720-5133

## Facsimile No.

858 720-5125

## Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned  
☐ the International Searching Authority ☒ the elected Offices concerned  
☐ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

## Authorized officer

Anman QIU

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 205271	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/14743	International filing date (day/month/year) 26/05/2000	Priority date (day/month/year) 28/05/1999
International Patent Classification (IPC) or national classification and IPC C12N5/00		
Applicant PACGEN TECHNOLOGIES LLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  21/12/2000	Date of completion of this report  17.09.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Roscoe, R  Telephone No. +49 89 2399 2554  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/14743

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

### Description, pages:

1-12 as originally filed

### Claims, No.:

19-37 as originally filed

1-18 as received on 09/07/2001 with letter of 06/07/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/14743

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**II. Priority**

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:  
**see separate sheet**

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-37
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-37

2. Citations and explanations  
**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/14743

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2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/14743

**I. Basis**

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

**II. Priority**

The priority document and the application are essentially identical. Hence, all claims entitled to priority from 28.05.99. Thus D7 is not relevant in the International Phase.

**V. Reasoned statement on Novelty, Inventive Step and Industrial Applicability**

**- Novelty (Art.33(2) PCT)**

D1 discloses a composition for treating wounds (examples deal with burn wounds to skin) comprising administration of fibroblasts having a transgene encoding a wound-healing enhancing cytokine and any other component enhancing healing. Autologous fibroblasts can be used (p.2, l.59.60), but preferably immortalized line (p.2, l.67) as in the examples. It seems that the primary function of the fibroblasts is to assist keratinocyte growth, and where allogeneic fibroblasts are used it is considered prudent to irradiate them prior to use so that they die relatively quickly following administration.

D2 refers to the use of hyaluronic acid based membranes seeded with autologous fibroblasts to treat burns. The preparation of the fibroblasts is not detailed, except that initiate culture from victims own skin.

D3 discloses treatment of burns using a collagen-glycosaminoglycan membrane seeded with autologous keratinocytes and fibroblasts. The membrane comprises the fibroblasts and is coated with layers of keratinocytes.

D4 discloses the use of fibroblast-seeded dermal substitutes for treating burns. Fibroblasts are obtained from autologous tissue i.e. (i) subdermal fat tissue, or (ii)

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/14743

debrided burn tissue.

D5 discloses a variety of different types of skin substitutes which use allogeneic fibroblasts. The reasoning behind choosing autologous or allogeneic cells is disclosed on p.806, top col.2. Provides general background information.

D6 discloses introduction of fibroblasts derived from rabbit ear skin (i.e. autologous) into transparent ear chambers implanted in rabbit ears, to study the effect on wound healing in these chambers.

It is noted that a blister resulting from a burn could probably be considered as a fistula (applicant may wish to comment on this). However, where treatment of burns is considered, it seems that the blistered skin would either be removed first, or the blister itself would not be treated in the abovedescribed prior art.

The addition of the feature "in the form of an injection" to claim 1 has rendered the novelty objections raised in the written opinion no longer relevant.

- **Inventive Step (Art.33(3) PCT)**

With regard to claims encompassing wound healing of an epithelial wound on the surface of the body, inventive step was not acknowledged. This applied to previous claims 1-9. Further, closure of any wound (i.e. gastric ulcer) can be considered obvious by this method since it would seem to be no different from using a skin fragment to close such a shallow wound. However, applicant has now introduced the feature of injection of the fibroblasts into the claims in question. This feature distinguishes from the mere administration of a skin graft. Hence, claims 1-15 are now considered inventive.

No prior art has been found showing that a skin graft would be suitable for the treatment of a fistula - presumably because the underlying problem would remain. Hence, consideration of graft technology does not render it obvious to use a method comprising fibroblasts for this purpose. Applicant himself refers to the use of sealants (bottom p.2, application) to treat fistulas, yet this has met with limited success, and there is no indication to use fibroblasts.



- **Industrial Applicability (Art.33(4) PCT)**

For the assessment of the present claims 1-37 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 1-37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**VI. Certain documents**

In accordance with Rule 70.10, PCT, applicants attention is drawn to the following document(s):

D7: WO-A-99/60951 (Publication date, 02.12.99; Priority date, 22.05.98; Filing date, 21.05.99)

It is noted that D7 would provide valid prior art for the assessment of novelty under Art.54(3) EPC, should present application be entered into a European Regional Phase. D7 discloses matrices wherein passaged autologous fibroblasts have been incorporated for use in tissue regeneration, but also direct (matrix-free) injection of such fibroblasts. Uses include treatment of ulcers and venous stasis.

Replaced  
by Art. 34  
Amendment  
WO 00/73418

WHAT IS CLAIMED IS:

1. A method of promoting wound healing in an animal, wherein said wound is susceptible to healing upon administration of autologous fibroblasts,  
5 which method comprises:

(a) obtaining autologous fibroblasts, and

(b) administering the autologous fibroblasts to a wound in said animal,  
wherein said autologous fibroblasts promote healing of the wound.

10 2. The method of claim 1, wherein said animal is a human.

3. The method of claim 2, wherein said autologous fibroblasts are derived from a tissue which is the same type of tissue as a tissue of which the wound is comprised.

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4. The method of claim 2, wherein said fibroblasts are cultured in the animal's own serum.

5. The method of claim 2, wherein said fibroblasts are passaged in culture  
20 less than about ten times.

6. The method of claim 5, wherein said fibroblasts are passaged in culture from about four to about six times.

25 7. The method of claim 2, wherein about 20 million autologous fibroblasts are administered per administration.

8. The method of claim 2, wherein said wound is a chronic non-healing wound.

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9. The method of claim 2, wherein said wound is an epithelial wound.

10. The method of claim 9, wherein said wound is due to venous stasis.

5 11. The method of claim 2, wherein said wound is a muscosal wound.

12. The method of claim 11, wherein said wound is due to a gastric ulcer.

10 13. The method of claim 12, wherein said autologous fibroblasts are administered by endoscopic injection.

14. The method of claim 11, wherein said wound is due to a duodenal ulcer.

15 15. The method of claim 11, wherein said wound is an anal fissure.

16. A method of promoting fistula healing in an animal, wherein said fistula is susceptible to healing upon administration of autologous fibroblasts, which method comprises:

20 (a) obtaining autologous fibroblasts, and  
(b) administering the autologous fibroblasts to a fistula in said animal, wherein said autologous fibroblasts promote healing of the fistula.

17. The method of claim 16, wherein said animal is a human.

25 18. The method of claim 17, wherein said autologous fibroblasts are derived from a tissue which is the same type of tissue as a tissue in which the fistula exists.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>205271</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 14743</b>	International filing date ( <i>day/month/year</i> ) <b>26/05/2000</b>	(Earliest) Priority Date ( <i>day/month/year</i> ) <b>28/05/1999</b>
Applicant <b>PACGEN TECHNOLOGIES LLC</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

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☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/14743

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K35/12 C12N5/08 A61P17/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, LIFESCIENCES, EMBASE, SCISEARCH, BIOSIS, WPI Data, EPO-Internal, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 197 16 098 A (UNIV LUDWIGS ALBERT) 22 October 1998 (1998-10-22) page 2, line 22-25 page 4, column 17 claims 1,12	1-9
A	---	16-37
X	HARRIS P A ET AL: "Use of hyaluronic acid and cultured autologous keratinocytes and fibroblasts in extensive burns 'letter!." LANCET, (1999 JAN 2) 353 (9146) 35-6. , XP002155960 the whole document ---	1-7
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

19 December 2000

Date of mailing of the international search report

08/01/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
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Authorized officer

Covone, M

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HANSBROUGH J F ET AL: "BURN WOUND CLOSURE WITH CULTURED AUTOLOGOUS KERATINOCYTES AND FIBROBLASTS ATTACHED TO A COLLAGEN GLYCOSAMINOGLYCAN SUBSTRATE" JAMA (JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION), vol. 262, no. 15, 1989, pages 2125-2130, XP000971590 ISSN: 0098-7484 the whole document	1-7
A	---	8-35
X	VAN ZUIJLEN P.P.M. ET AL: "Practical sources for autologous fibroblasts to prepare a bioengineered dermal equivalent '1!.' BURNS, (1998) 24/7 (687). , XP000971603 the whole document	1-7
A	---	
A	MANSBRIDGE J.: "Skin substitutes to enhance wound healing." EXPERT OPINION ON INVESTIGATIONAL DRUGS, (1998) 7/5 (803-809). , XP000971597 abstract page 807, left-hand column, paragraph 2	1-37
A	---	
A	KON K ET AL: "Transformation of fibroblasts into endothelial cells during angiogenesis." CELL AND TISSUE RESEARCH, (1994 DEC) 278 (3) 625-8. , XP000971600 the whole document	1-37
P,X	---	
P,X	WO 99 60951 A (ISOLAGEN TECHNOLOGIES INC) 2 December 1999 (1999-12-02) page 8, line 30 -page 9, line 21 claims -----	1-15

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/14743

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19716098 A	22-10-1998	AU 7215098 A WO 9848012 A EP 0975756 A	13-11-1998 29-10-1998 02-02-2000
WO 9960951 A	02-12-1999	AU 4093399 A	13-12-1999